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A REVIEW OF COUMARIN DERIVATIVES AND ITS BIOLOGICAL ACTIVITIES

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ABSTRACT

The coumarin chemically known a (benzopyran-2-one, or chromen-2-one) oxygen heterocyclic ring system, Coumarin is plant flavonoids widely distributed in nature. Natural coumarins are known to have antidiabetic activity, anabolic antioxidant and hepato protective activities. present in natural products (such as the anticoagulant warfarin) that display interesting pharmacological properties), which have been found to be useful in photochemotherapy, antitumor and anti-HIV therapy, and as stimulants for central nervous system, antibacterials, anti-inflammatory, anti-coagulants, and dyes. Of particular interest in breast cancer chemotherapy, some coumarins and their active metabolite 7-hydroxycoumarin analogs have shown sulfatase and aromatase inhibitory activities. Coumarin based selective estrogen receptor modulators (SERMs) and coumarin-estrogen conjugates have also been described as potential antibreast cancer agents. Therefore, the objective of this review is to focus on important coumarin analogs with biological activitie.

KEYWORD:- Coumarin, Biological activity, Antibacterial, Ant retroactivity, Green synthesis.

INTRODUCTION OF COUMARIN

Coumarin chemically known as 2H-1-benzopyran-2-one was first identified in 1820's as an oxygen heterocycle that is famous for its vanilla like or freshly – mowed hay fragrance.[1]

Coumarins are the simple compounds belonging to a large class of molecules known as benzopyrones. Furthermore, coumarins and their derivatives form an elite class of compounds, occupying an important place in the realm of natural products and synthetic organic chemistry.[2]

Benzopyrones are a group of compounds whose members include Coumarins and flavonoides hugely distributed in plants. Till now, more than 1300 coumarins were identified from natural sources. These natural compounds serve as important models for advanced design and synthesis of more active coumarins analogous and were shown various pharmacological activities.[3]

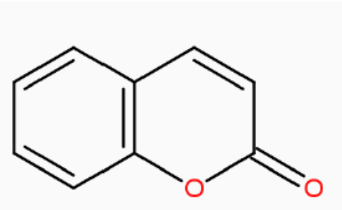
Coumarins (2H-1-benzopyran-2-ones) are important oxygen containing fused heterocycles used in drugs and dyes. Coumarins be bound their class name to 'coumarou' the vernacular name of the Tonka bean (*Dipteryx odorata willd, Fabaceae)*, from which coumarin itself was isolated in 1820. They are the family of lactones containing benzopyrone skeletal framework that have enjoyed isolation from plant as well as total synthesis in the laboratory. The incorporation group as a fused component into parent coumarin alters the property of parent coumarin and converts it into a more useful product. Coumarin is plant flavonoids widely distributed in nature. Natural coumarins are known to have antidiabetic activity, anabolic antioxidant and hepato protective activities.[4]

Substituted coumarins derivatives have been reported to have variety of biological activities. The potent antibiotics like Novobiocin, Coumaromycin and Chartesium are coumarin derivatives. Recently, the interest on these compounds has been revived owing to their use as fluorescent markers in the biochemical determination of enzymes.

Coumarin derivatives can be synthesized by one of such methods as the Claisen rearrangement, Perkin reaction, Pechmann reaction, Witting reaction, as well as the Knoevnagel condensation. Derivatives of coumarins usually occur naturally as secondary metabolite present in seed, roots and leaves of many plant species. Microwave irradiation has since been proven to be extremely useful for promoting and simplifying many condensation reactions which can be carried out both in solvent and under solvent free condition. The essence of this work was synthesis of coumarin derivatives using microwave irradiation in comparison with conventional methods. These investigations have revealed their potentials as versatile biodynamic agent for example-3-heteroaryl substituted coumarin and

benzocoumarins of potential interest as pharmaceuticals and photochromic dyes. Similarly various coumarin chalcones in the solvent free media exhibit high potency as antibacterial agent.[15] Coumarins compounds are an important class of oxygen-containing heterocyclic moiety originally found as secondary metabolites in some microorganisms and plants. Large numbers of organic compounds containing coumarin as a basic unit have been found many important applications, such as anti-inflammatory, antibacterial, analgesic, antifungal, antioxidant, anticancer, antimicrobial and anti-HIV. Along with these applications, coumarin compounds have widely applied in other fields, such as food and dyes industries fragrance and cosmetic.[5]

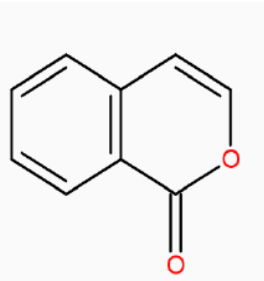
There are four main coumarin sub-types: the simple coumarins, furanocoumarins, pyranocoumarins and the pyrone-substituted coumarins (The simple coumarins (e.g. coumarin, 7-hydroxycoumarin and 6,7- dihydroxycoumarin), are the hydroxylated, alkoxylated and alkylated derivatives of the parent compound, coumarin, along with their glycosides. Furanocoumarins consist of a five-membered furan ring attached to the coumarin nucleus, divided into linear or angular types with substituents at one or both of the remaining benzoid positions. Pyranocoumarin members are analogous to the furanocoumarins, but contain a six-membered ring. Coumarins substituted in the pyrone ring include 4 hydroxycoumarin.[3] The synthetic compound, warfarin, belongs to this coumarin subtype. By virtue of its structural simplicity coumarin has been assigned as head of the benzo-a pyrones, although it is generally accepted that 7-hydroxycoumarin be regarded as the parent compound of the more complex coumarins.[6]



Coumarin

or

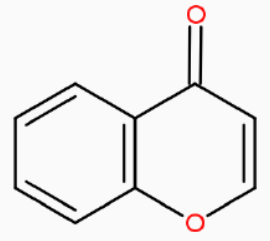
2H-1- benzopyran -2-one



Chromone

or

4H-1-benzopyran-4-one



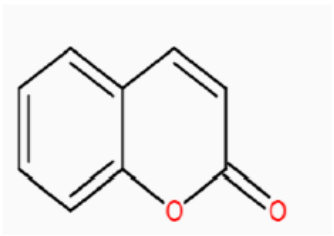
Isocoumarin

or

1H-2-benzopyran-1-one

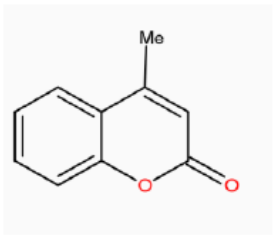
Fig. 1: Coumarine, Chromone, & Isocoumarine.

Three target molecules, namely coumarin, 4-methylcoumarin and flavones [2- phenylbenzo-4-pyrone, are used to illustrate typical cyclisation reactions.



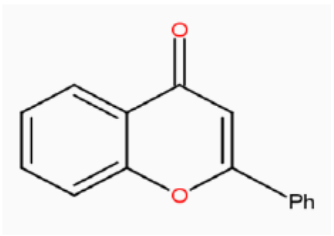
(A)

Coumarin



(B)

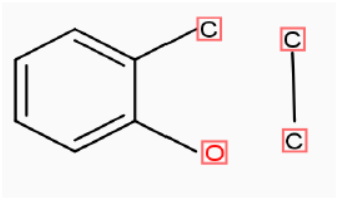
4-methylcoumarin



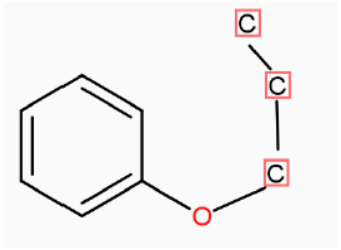
(C)

Flavone (2-phenylbenzo-4-pyrone)

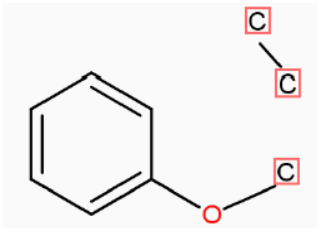
Overall strategies for cyclisation are of the type illustrated D, E



(D)

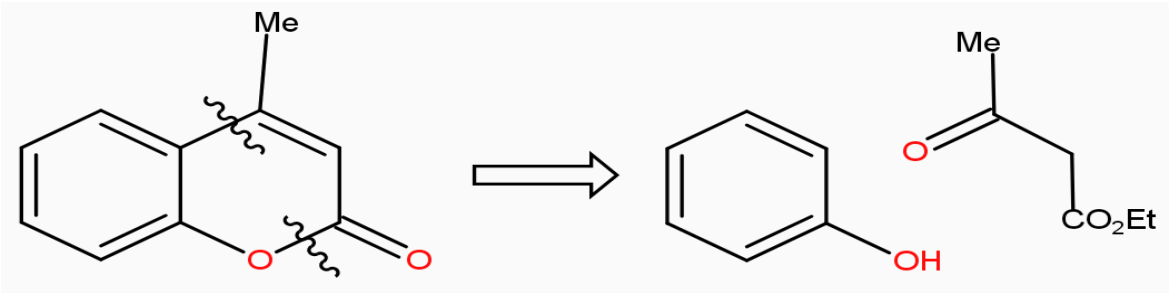


(E)

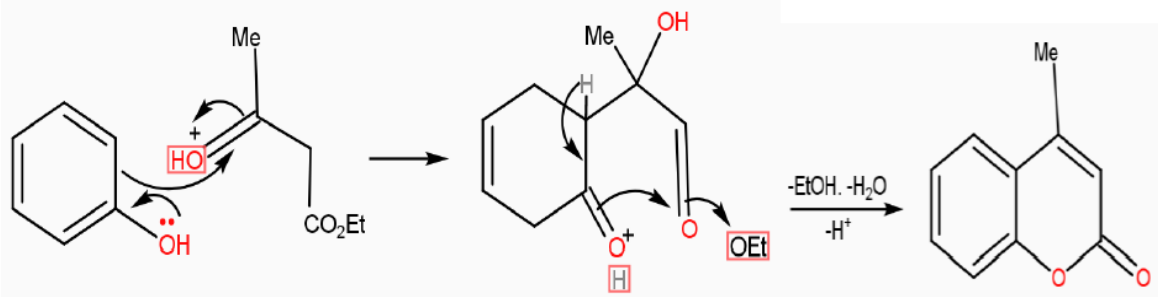


(F)

A more general synthesis of coumarins involves the interaction of a phenol with a beta ketoester in the presence of an acid condensing agent (The pechmann reaction). In the case of 4-methyl coumarin appropriate disconnection reveals ethyl acetoacetate and phenol.



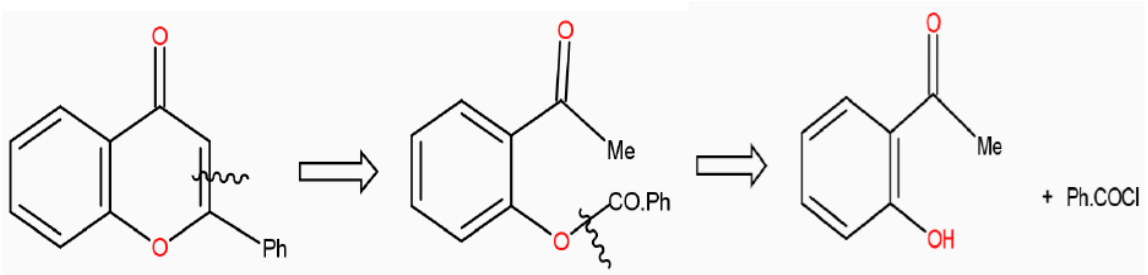
Concentrate sulphuric acid is generally used as the condensing agent for simple monohydric phenols and beta ketoesters, although phenol itself reacts better in the presence of aluminium chloride. The mechanism of the reaction is thought to involve the initial formation of a beta-hydroxy ester, which then cyclises and dehydrates to yield the coumarin.



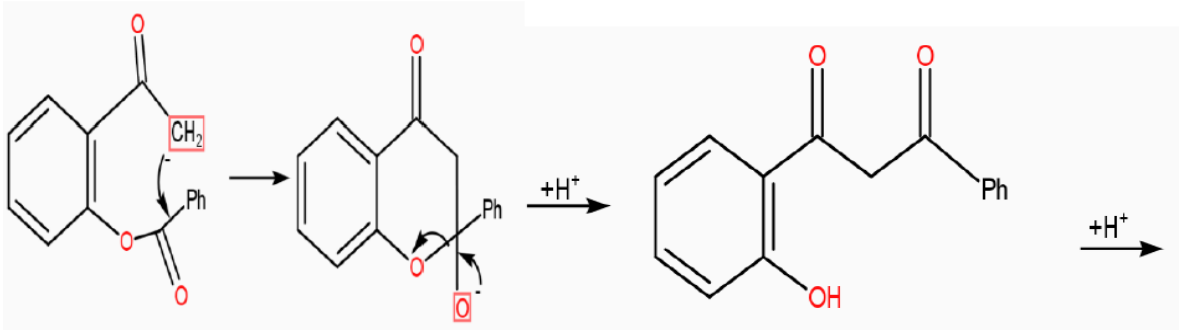
Polyhydric phenols, particularly when the two hydroxyl groups are meta oriented, react with great ease. If sulphuric acid is used as the condensing agent, careful temperature control is needed to ensure a good yield. In these cases the use of polyphosphoric acid is recommended and this alternative process is illustrated. Good yield are also obtained from polyhydric phenols by condensation in the presence of trifluoroacetic acid.

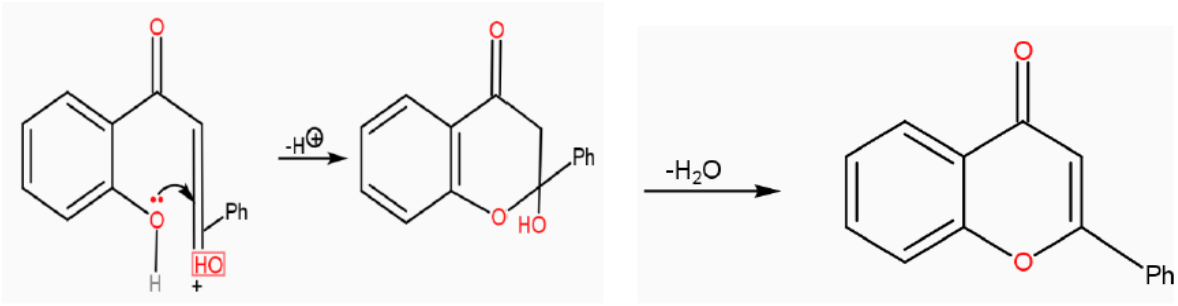
A retrosynthetic analysis for flavone reveals o-benzoyloxyacetophenone, readily formed by the benzoylation of o-hydroxyacetophenone.

Pharmacological activity



In practice the cyclisation of takes place in two stages. Initially a base – catalysed rearrangement converts into o-hydroxydinbenzoylmethane which may be isolated, and then cyclised in the presence of acid to flavone.[7]





Physico chemical properties of coumarin

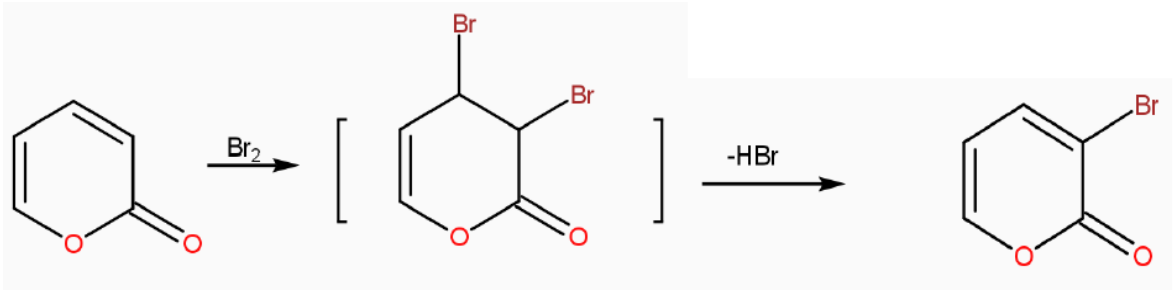
Physical properties of coumarin

Molecular formula	**$C_6H_9O_2$**
Molar mass	146.14g/mol
Density	935 kg/m^3
Melting point	71 ^0C
Boiling point	301.7 ^0C
Solubility	Soluble in water, ethanol very soluble in ether , chloroform

(A) Reactivity of coumarin molecule:- Both alfa and gama-pyromes are potentially aromatic but the latter are more stable tha former. Alfa-pyrone itself polymerizes slowely on standing while the gama-pyrones are quite stable crystalline substances.

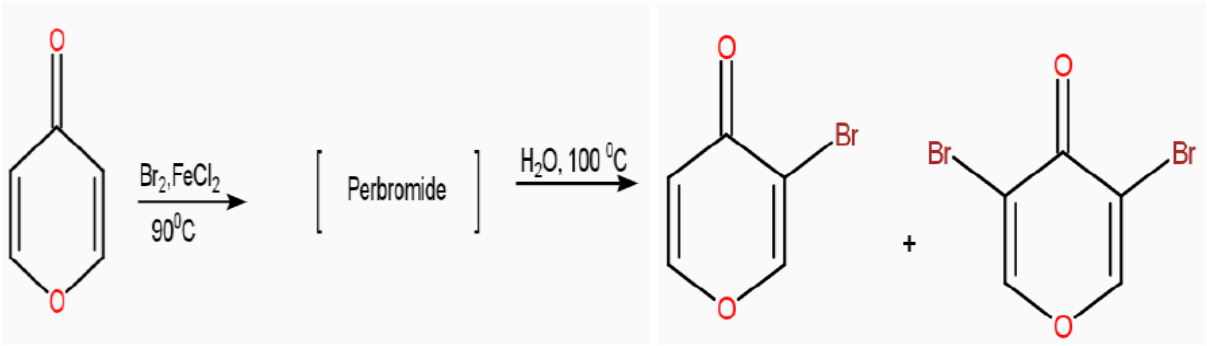
a. Electrophilic Substitution: The aromatic character of pyrones is reflected in the their reactive towards electrophilic substitution. Both α– and-γ pyrones undergo substitution at 3-or 5-position, i.e. o-or p-to the carbonyl group. The ease of electrophilic substitution is enhanced by the presence of alkyl substituents on the ring.

- **Halogenation:** α pyrone is brominated at the 3-position via an addition elimination eaction and is not the result of direct electrophilic substitution.

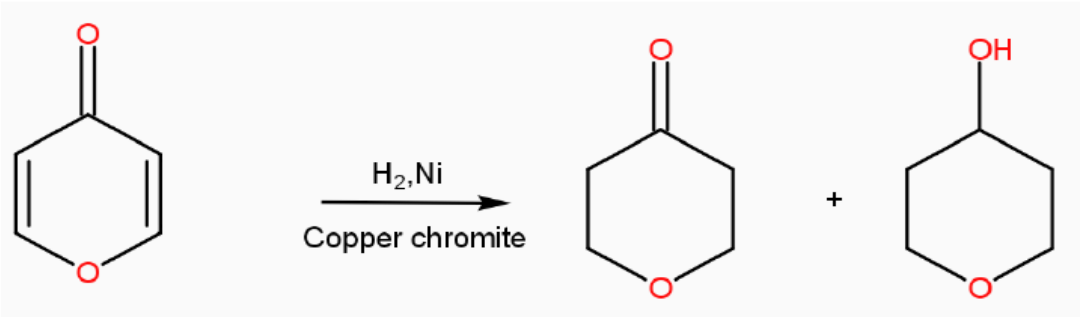


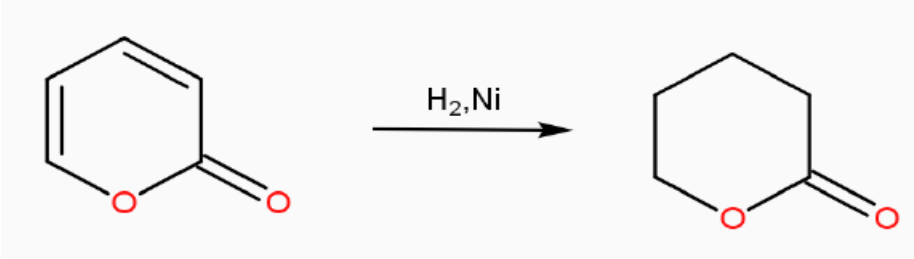
The ring can nitrated and sulfonated. Reaction of α – pyrone with nitronium tetrafluoroborate, reversibly form a o- nitro salt which is slowly converted to 5-nitro-α-pyrone.

Bromination of γ-pyrone yields a mixture of mono-and di-bromo γ-pyrones via a perbromide formation.

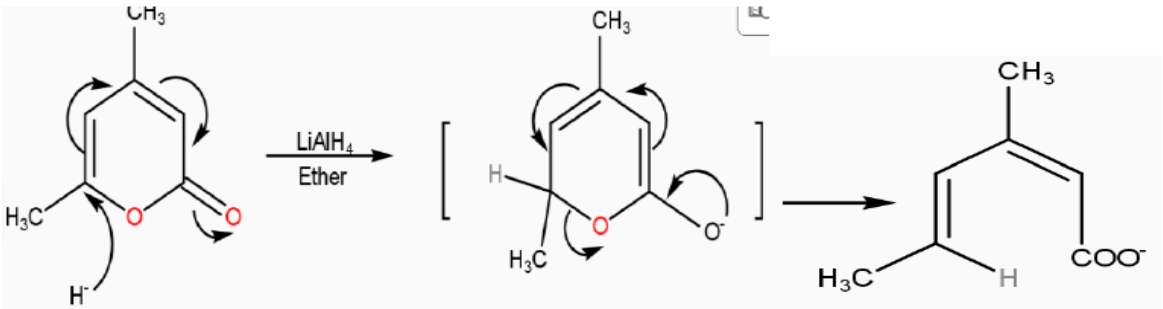


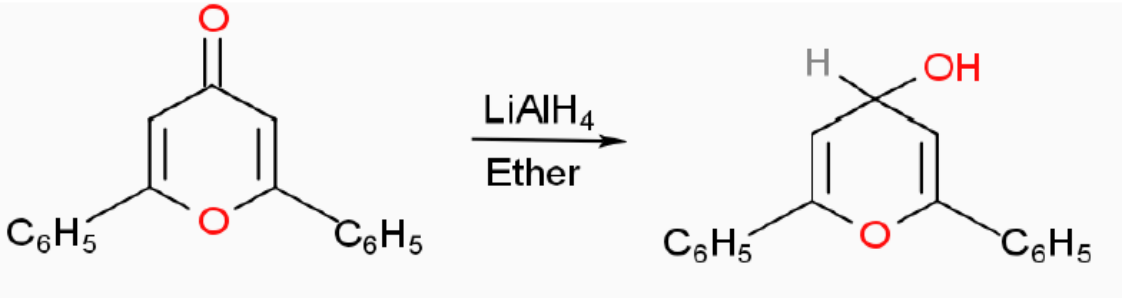
b. Reaction with reducing agents: Catalytic hydrogenation (H2, Ni) equation and occurs at the C-C double bonds to give saturated lactone. Hydrogenation further supports the olefinic nature of both α- and γ-pyrones.



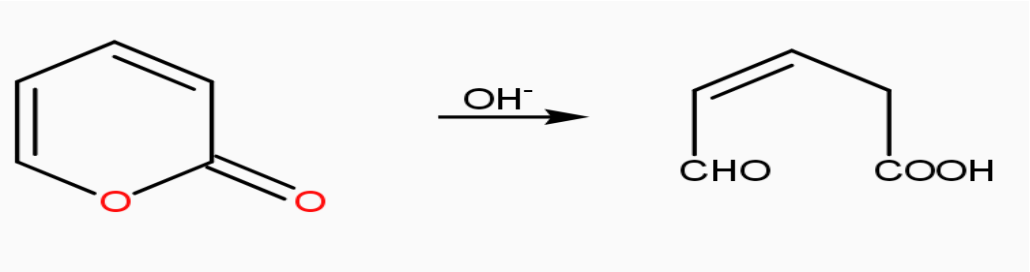


Sodium Borohydride does not react with pyrones but lithium aluminium hydride break the a-pyrone ring to form an acid but an alcohol is obtained in the case of g - pyrone, due to reduction of the carbonyl moiety.

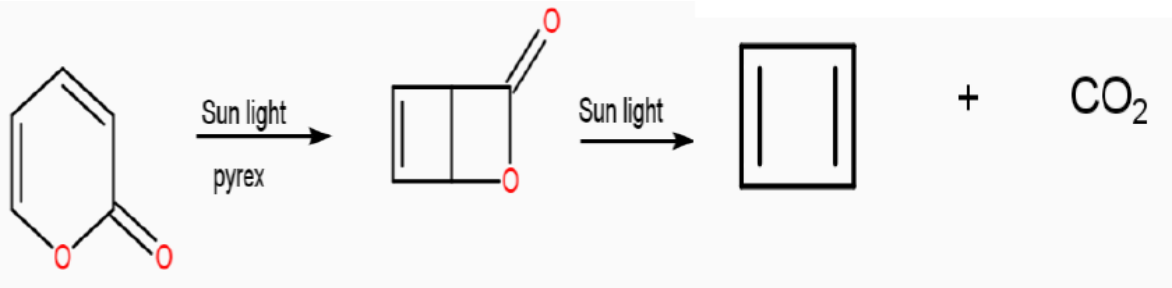


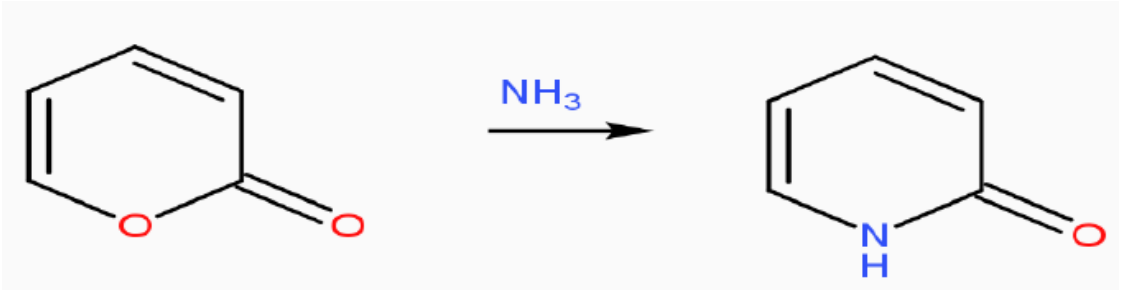


c. **Nucleophilic reaction:** In marked contrast to electrophilic substitution, pyrone are easily attacked by nucleophilic reagent. Weak nucleophiles add at the 2-position while strong ones at the 6- position.



d. **Photochemical reaction:** Pyrones have been widely investigated photochemically and they have been shown to give interesting products. On photolysis α-pyrone loses carbon dioxide to yield cyclobutadiene.[8]

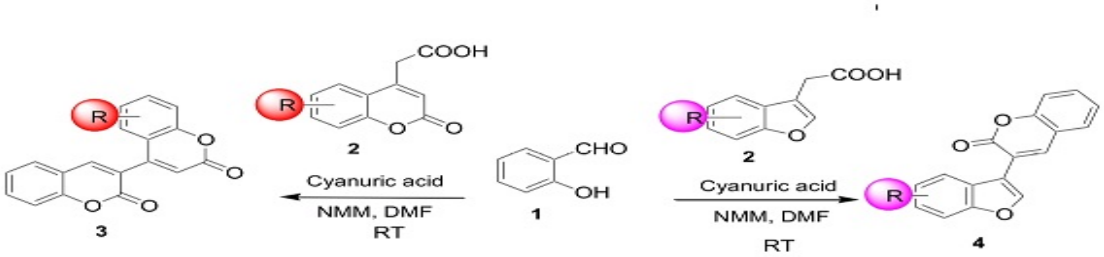




Mustafa1 Fakri Yasser, Bashir Kahtan Moath, Oglah Khudhayer Mahmood, "has been reported the Original and Innovative Advances in the Synthetic Schemes of Coumarin-Based Derivatives:, and Coumarin, a chemical nucleus, is award gifted rom nature. This description

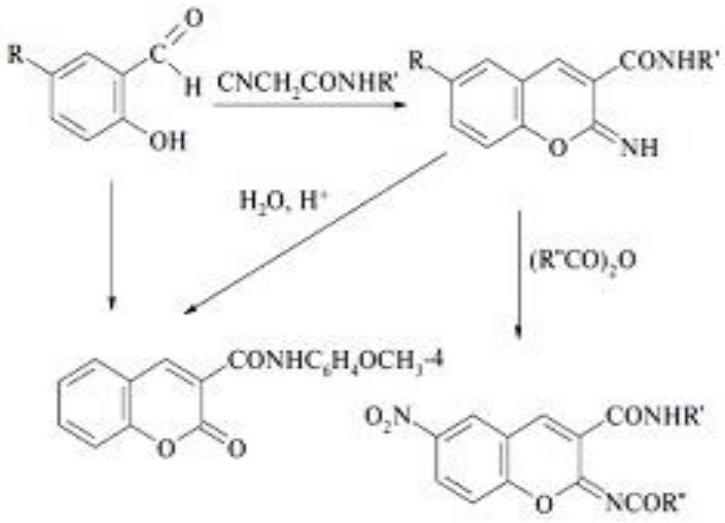
is due to the versatile of its derivatives and the wide variety of their biological activities. This review was focused on the traditional synthetic routes of coumarins and their innovative improvements as well as the benefits arising from the use of each of them.[9]

Hunagund Umesh, Shaikh Farzanabi, Shastri A. Lokesh, "has been Synthesis of a new series of novel bicoumarin and 3-(3-benzofuranyl) coumarin derivatives and play an important role in organic electronic applications.[10]

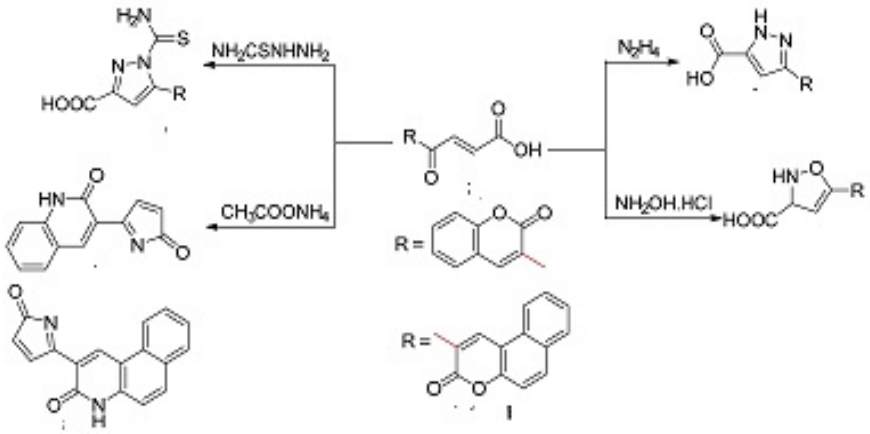


Scheme Synthesis of bicoumarins and 3-(3-benzofuranyl)coumarins

Salaskar P. Pooja, Bairagi H. Shriram, Loke D. Sonal, Surve N. Nilam, Tandel V. Darshana**,** have been reported Coumarin is a chemical compound found in many plants. It is a bitter in taste, appetite suppressant, and is probably produced by plants as a defense chemical to discourage predation. The most useful method for the synthesis of Coumarin is fromphenol and ethyl acetate and also by using catalyst. Coumarin is used in the pharmaceutical industry as a precursor moleculein the synthesis of a number of synt even more potent rodenticide.[11]

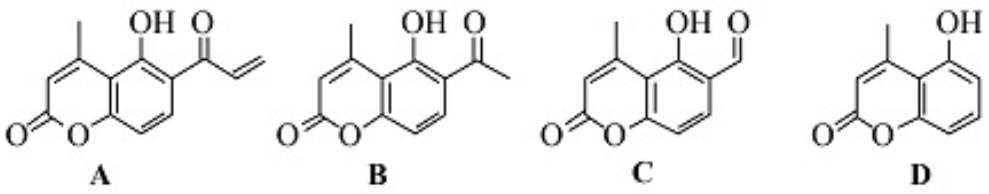


Khaldi-Khellafia Nassima, Oukacha-Hikem Djamila have been reported "Green synthesis, characterization, structure, biological activity, Most of the coumarins exhibited significant antibacterial activity against *S. aureus* Gram-positive bacteria compared to Cefotaxime as positive control.[2]

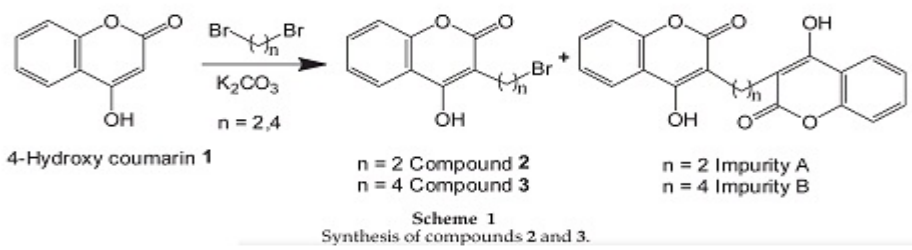


Scheme: Synthesis of compounds

V.K, Srivastav Tiwari M., X. Zhang and Yao x-j have been repoted. "Synthesis and Antiretroviral Activity of 6-Acetyl-coumarin Derivatives against HIV-1 Infectio.[13]

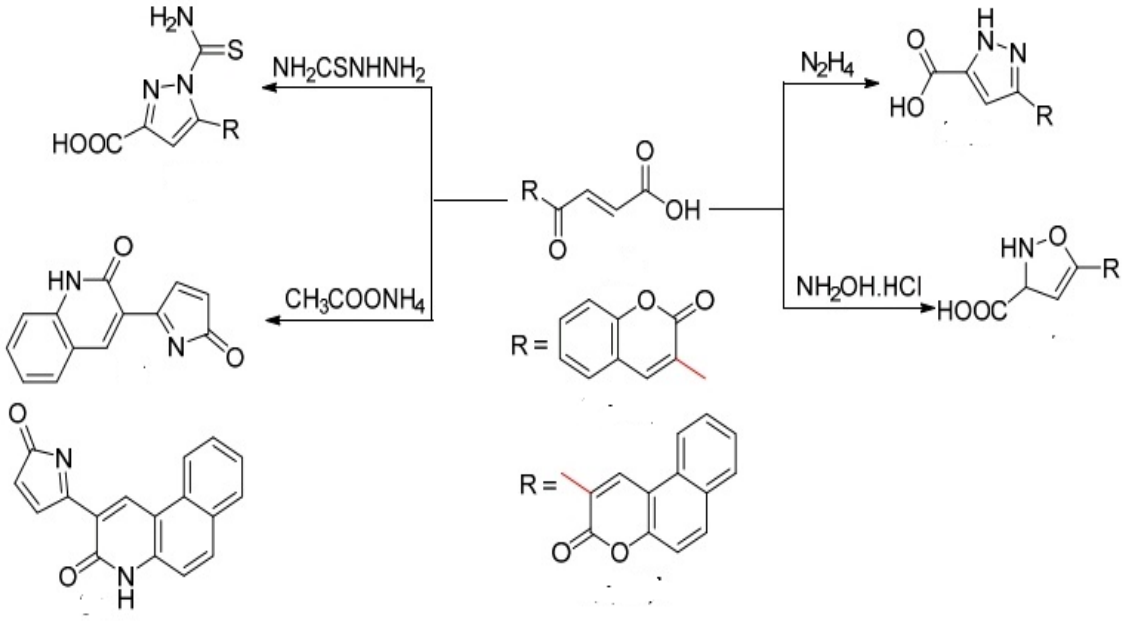


Naik G. Chirag Malik M. Gulam, Parekh M. Hitesh, have a novel series of Coumarin Derivatives: Synthesis, Characterization and Antimicrobial Activity.[14]



Scheme 1
Synthesis of compounds 2 and 3.

Salem A. I. Mounir, Marzouk I. Magda, have been reported the Synthesis and Characterization of Some New Coumarins with In Vitro Antitumor and Antioxidant Activity and High Protective Effects against DNA Damage.[15]



Scheme 2. Synthesis of compounds

CONCLUSION

This paper covers natural coumarin lead compounds and their broad pharmacological properties antibacterial, antiretrovirus, antidiabetic, anticoagulant. Natural coumarins are of great interest due to their widespread pharmacological properties.

ACKNOWLEDGMENTS

The authors thank swamivivekand collage of pharmacy for facilities and mis. RUPALI grateful thanks for supporting my review paper.

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